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Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MDWC-05
P.O. Box 12233
Research Triangle Park, NC 27709

Via Fax: 919-541-2242

Re: Call for Public Comments
Revision of Classification of 2,3,7,8 TCDD

Dear Dr. Jameson:

This responds to the National Toxicology Program ("NTP") request for comments with respect to the proposed classification of 2,3,7,8-tetrachlorodibenzo-p-dioxin ("TCDD") in NTP's Report on Carcinogens, Ninth Edition. NTP proposes to upgrade the classification of TCDD from "reasonably anticipated to be a human carcinogen" to "known to be a human carcinogen." 62 Fed. Reg. 37272, 37273 (July 11, 1997). We believe that the proposal does not comport with either the scientific evidence or NTP's criteria for classification of substances as known carcinogens, and we urge NTP not to adopt the proposed change.

NTP's proposal is not accompanied by any explanation or rationale. We understand, however, that the proposal has been prompted by the recent review of TCDD by the International Agency for Research on Cancer ("IARC"). IARC's monograph covering TCDD has just been released.

IARC has found that "There is *limited evidence* in humans for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin." IARC Monographs, volume 69, at page 342 (emphasis in original). The IARC Working group was unable to find sufficient evidence of human carcinogenicity, even though it considered all available epidemiologic evidence. We are not aware of any new evidence since the recent IARC conclusion that

would support a finding of sufficient human evidence of carcinogenicity.

IARC's decision to label TCDD in IARC's Group 1 as an overall evaluation was based on the limited human evidence and additional "supporting evidence" including information that TCDD acts through a mechanism involving the Ah receptor. IARC did not, however, find that the mechanism of TCDD carcinogenicity in animals has been identified or explained. We do not believe that IARC's use of "supporting" evidence justifies the overall IARC classification.

In any event, however, NTP's criteria do not allow for the use of mechanistic or other relevant data to upgrade a classification to "known to be a human carcinogen." In the public notice announcing NTP's Revised Criteria and Process for Listing Substances in the Biennial Report on Carcinogens, 61 Fed. Reg. 50499 (Sept. 26, 1996), NTP announced revised criteria for both the "known to be a human carcinogen" category and the "reasonably anticipated" category. NTP set out the revised criteria for the known category as follows:

> There is sufficient evidence of carcinogencity from studies in humans which indicates a causal relationship between *exposure to* the agent, *substance or mixture* and human cancer. (Emphasis in original, showing revisions from former criteria.)

NTP did not revise its longstanding requirement that classification as a known human carcinogen in the Report requires sufficient evidence from human studies.

With regard to the "reasonably anticipated" category, NTP in its 1996 criteria announced several revisions. Among the changes, NTP added the following criterion for classification as "reasonably anticipated to be a human carcinogen":

> There is less than sufficient evidence of carcinogencity in humans or laboratory animals, however . . . there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

61 Fed. Reg. at 50500. Thus, NTP was explicit that mechanistic information may serve as the basis for classification of a substance as "reasonably anticipated to be a human carcinogen," in contrast to the requirement of human evidence for classification in the "known" category.

Also as part of the 1996 revision to the "reasonably anticipated" criteria, NTP added a paragraph noting that NTP will consider all relevant evidence, including information such as dose-response, route of exposure, pharmacokinetics, or other mechanism data. Id. This new paragraph is clearly set out in the *Federal Register* under the heading of the "reasonably anticipated" criteria. The paragraph regarding use of supporting relevant evidence does not modify the criteria for the "known to be a human carcinogen" category, which are set out under a separate heading in the *Federal Register*.

There is nothing in the revised criteria suggesting that supporting evidence can be used to justify classification as a "known" human carcinogen where epidemiologic evidence is limited or insufficient. (IARC, in contrast, expressly adopted criteria under which supporting evidence can be used to adopt an overall Group 1 classification. See IARC monographs, volume 69, p. 26.) Rather, NTP added explicitly the authority to use mechanistic evidence to justify only a "reasonably anticipated" classification.

Thus, we are surprised and puzzled by the Notice proposing a revision to the classification of TCDD. NTP has offered no explanation of how TCDD might meet the criteria for the "known" category: "sufficient evidence of carcinogencity from studies in humans which indicates a causal relationship." 61 Fed. Reg. 50499. Nor has NTP offered any reason why limited human evidence combined with mechanistic information would not fall in the "reasonably anticipated" category as it is now expressly defined. IARC's recent finding that the human evidence is "limited" strongly supports maintenance of NTP's current classification of TCDD as only "reasonably anticipated."

If NTP intends to disagree with IARC's evaluation of the human evidence, then we respectfully request that NTP explain the basis for such a position and provide an opportunity for comment. Otherwise, we would urge NTP to follow faithfully its own stated criteria for classification.

We appreciate your consideration of these comments.

Sincerely,

John L. Festa, Ph.D.
Senior Scientist